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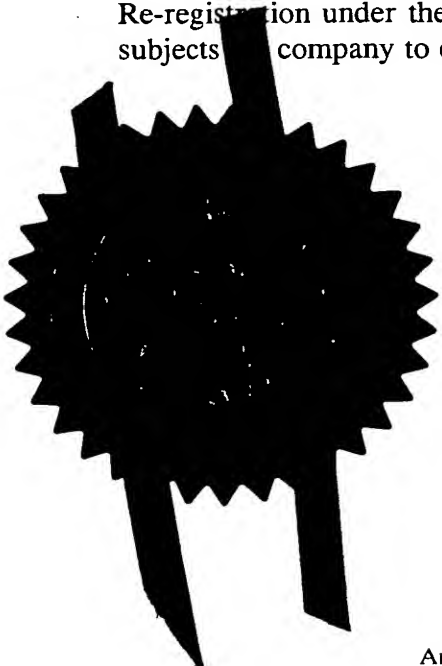
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Signed

AmBrewer

Dated 24 August 2000

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GB9920296.2

By virtue of a direction given under Section of the Patents Act 1977, the application is proceeding in the name of

ASTRAZENECA AB,
Incorporated in Sweden,
S-151 85 Sodertalje,
Sweden

[ADP No. 07822448003]

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GB9920296.2

By virtue of a direction given under Section of the Patents Act 1977, the application is proceeding in the name of

ASTRAZENECA UK LIMITED
Incorporated in the United Kingdom
15 Stanhope Gate
LONDON
W1Y 6AZ
United Kingdom

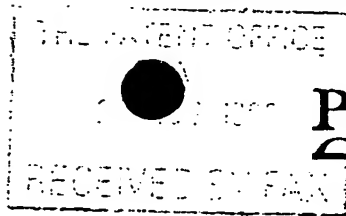
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SECTION 9(1) 1977 ACT APPLICATION FILED 14/7/2000

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The Patent Office

Cardiff Road
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1. Your reference

PHM99-136/GB/P

27 AUG 1999

2. Patent application number

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9920296.2

27AUG99 E472741-1 002934

P01/7700 A 02 002934 2

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Zeneca Limited

15 Stanhope Gate

LONDON W1V 6LN

Great Britain

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

6254007002

SECTION 30 (1) APPLICATION FILED 9/3/00.

4. Title of the invention

NEW CATALYST

5. Name of your agent (if you have one)

DENERLEY, Paul Millington

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Global Intellectual Property, Patents
AstraZeneca PLC
Mersey, Alderley Park
Macclesfield, Cheshire, SK10 4TG
Great Britain

Patents ADP number (if you know it)

1030618002

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Country

Priority application number
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Date of filing
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Number of earlier application

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Description

10

Claim(s)

Abstract

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

Lynda M Slack

Date

27 Aug 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

MRS LYNDA M SLACK - 01625 516173

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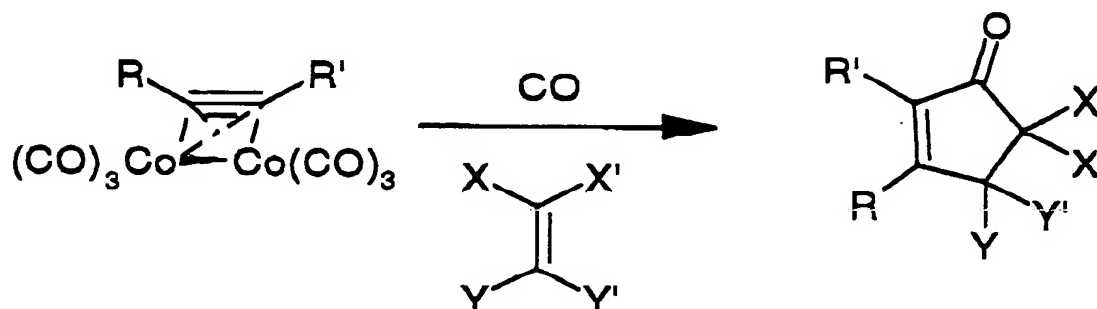
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New Catalyst

The reaction between an π -alkynedicobalt hexacarbonyl complex, an alkene, and carbon monoxide to produce a cyclopentenone is generally referred to as the Pauson-Khand reaction (P.L. Pauson, *Tetrahedron*, 1985, 41, 5860) (Scheme 1).

5



Scheme 1: Pauson Khand reaction

- 10 The products of the Pauson-Khand reaction are in general chiral except in the case of certain symmetrical alkenes ($X=X'$ and $Y=Y'$). If the components of the reaction are racemic or prochiral then chiral cyclopentenones produced by the reaction are produced in racemic form.

- The reaction succeeds for a wide range of substrates with the exception of tetrasubstituted alkenes, which are normally unreactive. The stereochemistry (e.g. M.E. Kraft, *J. Amer. Chem. Soc.*, 1988, 110, 968) and regiochemistry (e.g. K.H. Dotz and M. Popall, *Tetrahedron*, 1985, 41, 5797) of the reaction have been the subject of investigation, for instance in the case of unsymmetrical alkynes the larger substituent (e.g. R') generally forms the substituent at the α carbon of the cyclopentenone.

20

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In cases where the alkyne and alkene are both part of the same organic molecule the reaction forms two rings and where the olefin is itself cyclic tricyclic products are easily produced so that the reaction can give products of great complexity.

- 5 Accordingly the reaction is valuable because it makes complex organic molecules from simple components and these complex molecules are valuable *per se* or as intermediates for the production of high value-added products such as pharmaceuticals and fine chemicals.

- Mixtures of an alkyne, an alkene, and carbon monoxide can also be converted *in situ* into π -
10 alkynedicobalt hexacarbonyl complexes using stoichiometric amounts of dicobalt octacarbonyl or its tricobalt or tetracobalt homologues as part of the synthetic route leading to cyclopentenones.

- Substoichiometric amounts of dicobalt octacarbonyl or π -alkynedicobalt hexacarbonyl have
15 also been used to catalyse the formation of cyclopentenones from alkynes, alkenes, and carbon monoxide (e.g. I.U. Khand, G.R. Knox, P.L. Pauson, W.E. Watts, and M.I. Foreman, *J. Chem. Soc., Perkin Trans. I*, 1973, 977; D.B. Belanger, D.J.R. O'Mahoney and T. Livinghouse, *Tetrahedron Lett.*, 1998, 39, 7637; and D.B. Belanger and T. Livinghouse, *Tetrahedron Lett.*, 1998, 39, 7641).).

20

- Derivatives of π -alkynedicobalt hexacarbonyl complexes such as π -
alkynedicobaltcarbonylphosphine complexes have been used in the Pauson-Khand reaction (P.
Bladon, P.L. Pauson, H. Brunner and R. Eder, *J. Organometal. Chem.*, 1988, 355, 449) and
catalysis of the Pauson-Khand reaction using dicobalt octacarbonyl has been performed in the
25 presence of added ligands such as phosphites and phosphines (N. Jeong, S.H. Hwang, Y. Lee and Y.K. Chung, *J. Amer. Chem. Soc.*, 1994, 116, 3159). Heterobimetallic analogues in which a cobalt atom has been replaced by molybdenum are also known (D.T. Rutherford and S.D.R. Christie *Tetrahedron Lett.*, 1998, 39, 9805).

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We use the description "Pauson-Khand" reaction to include all reactions between carbon monoxide, alkenes, and alkynes that are promoted by transition metal complexes and that lead to cyclopentenone formation.

5

Although the Pauson-Khand reaction produces useful products it suffers from a number of drawbacks. Dicobaltoctacarbonyl and its analogues are volatile, toxic, and unstable both to loss of carbon monoxide and to aerial oxidation. Accordingly the cobalt carbonyl reagent poses hazards in storage, use, disposal, and product purification. For best results the commercial reagent often requires rigorous purification immediately before use (e.g. "Impure samples of commercial $\text{Co}_2(\text{CO})_8$ must be rigorously purified by recrystallisation from degassed HPLC grade hexane or room temperature sublimation at 50 mTorr immediately prior to use". T. Livinghouse, *Tetrahedron Lett*, 1998, 39, 7637). In addition, generally, the cyclopentenone product may retain metal impurities, especially when used stoichiometrically.

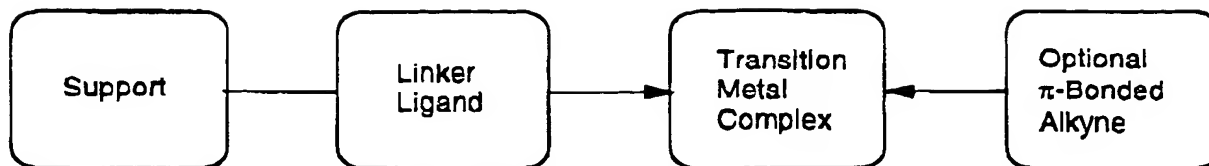
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We have recently described the use of immobilised transition metal complexes as traceless linkers for unsaturated organic molecules. A class of immobilised π -alkynedicobalt hexacarbonyl complexes as traceless linkers for alkyne derivatives were disclosed, in which an alkyne is immobilised using its π -alkynedicobalt hexacarbonyl complex as a traceless link with the expectation that the alkyne or its derivative would be liberated in at the end of a sequence of stoichiometric steps.

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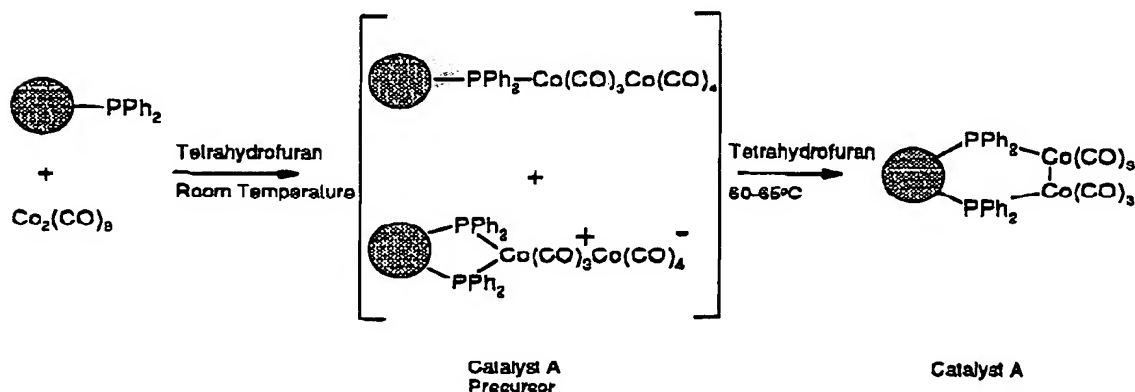
We have now found that immobilised cobalt carbonyl complexes prepared for use as traceless linkers are members of an advantageous class of catalysts that promote the Pauson-Khand reaction. The invention is illustrated below.

25



Where the Transition Metal Complex is a cobalt carbonyl or one of its analogues or derivatives
 5 drawn from the group of transition metal-ligand complexes known to promote the Pauson-Khand reaction.

For instance, the invention is illustrated below (Catalyst A) where the support is a cross linked polystyrene resin, the linker ligand is a triarylphosphine, and the transition metal complex is
 10 derived from dicobalt octacarbonyl. The representation of Catalyst A is schematic and is not intended to define the chemical constitution or the bonding of the catalytically active species.



15 The method of the invention offers considerable advantages. It is safe and convenient to use at all stages of the operation. The immobilised catalysts may be prepared in active form from commercially available precursors such as dicobalt octacarbonyl (Strem Chemical Co. Inc.) and they retain their activity for longer than their analogues that are not immobilised. The

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immobilised catalysts are not volatile and are easier to contain than their analogues that are not immobilised. Accordingly they are safer to use, store, and transport. The immobilised catalyst may also be easily recovered from the reaction, for example, by filtration so that valuable catalysts may be recovered for reuse, potential environmental contaminants may be easily
5 eliminated, and the product may be separated from potentially noxious transition metal carbonyl contaminants. Because the catalyst may be easily recovered for reuse the method of the invention enables the economic use of costly transition metal complexes designed to confer special benefits such as the production of enantiomerically pure or enriched cyclopentenones.

10 An example of the use of an immobilised catalyst is given in Scheme 2.

Presented as a first feature of the invention is the use of an immobilised cobalt carbonyl complex as a catalyst in a Pauson-Khand reaction.

15 The immobilised π -alkynecobaltcarbonyl complex may also be activated as a catalyst for the Pauson-Khand reaction by prior conversion into an alkyne complex. The alkyne may be one which is the same as the alkyne reagent used in the Pauson-Khand reaction or may be one which is readily displaced by the alkyne reagent used in the Pauson-Khand reaction and therefore will exchange with the alkyne reagent to form a complex with the cobalt.

20

Presented as a further feature of the invention is the use of an immobilised π -alkynecobalt carbonyl complex as a catalyst for the Pauson-Khand reaction.

A further feature is the use of immobilised analogues and derivatives of cobalt carbonyls and
25 their alkyne complexes as catalysts in a Pauson-Khand reaction.

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As discussed above, depending upon the starting alkene starting material, chiral centres may be found in the cyclopentenone product. However, typically, Pauson-Khand reactions produce racemic mixtures of any product with a chiral centre. In the prior art it is suggested that carbonylmetal complexes can be generated as catalysts for the Pauson-Khand reaction which will produce enantiomerically enriched products. This would be extremely valuable in the pharmaceutical and specialty chemical fields since enantiomerically pure products are desired. However, the drawbacks mentioned above make this prohibitively expensive. In addition any extra effort and expense in producing a complex chiral catalyst would be wasted since little of the original starting catalyst would be available for subsequent reactions. In the present invention the ability to recover a significant amount of catalyst allows increased and rewarding efforts to be made in preparing catalyst for the Pauson-Khand reaction which are able to produce enantiomerically enriched products.

The Pauson-Khand reaction is not limited to complexes of cobalt: other transition metals that are able to form π -alkyne and π -alkene transition metal carbonyl complexes in the presence of carbon monoxide, alkynes and alkenes are also able to promote cyclopentenone formation from carbon monoxide, alkynes, and alkenes. Such metals include other metals of the cobalt group, namely rhodium and iridium, from other groups such as; tungsten and molybdenum (T.R. Hoyer, J.A. Suriano *Organometallics*, 1992, 11, 2044, titanium (N.M. Kablaoui, F.A. Hicks, and S.L. Buchwald *J. Amer. Chem. Soc.*, 1996, 118, 5818), iron and ruthenium (T. Morimoto, N. Chatani, Y. Fukumoto, and S. Murai, *J. Org. Chem.*, 1997, 62, 3762).

Further features of the invention are the immobilised catalysts, their uses and processes, as defined above or below, in which one [or both] of the cobalt atoms is replaced by a metal independently selected from a transition group metal, preferably of the same periodic group as cobalt. Transition metals that are suitable for use in Pauson-Khand reaction are known to the skilled person or may be tested for their ability to catalyse a Pauson-Khand reaction. Suitable transition metals from the same periodic group as cobalt are selected from; rhodium and iridium; transition metals of other periodic groups include; titanium, ruthenium, tungsten, molybdenum, nickel, and iron.

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Immobilised heterobimetallic carbonyl complexes may be formed and these represent a further novel feature of the invention as being particularly useful for producing chiral catalysts of value in the production of enantiomerically enriched cyclopentenone products.

5

A further feature is the use of a resolved or partially resolved cobalt carbonyl complex wherein one of the cobalt atoms is replaced by different transition metal in a Pauson-Khand reaction to produce, preferably, a resolved or partly resolved product.

- 10 A further feature of the invention is a process for the preparation of a cyclopentenone compound or analogue thereof in a Pauson-Khand reaction, which comprises either;
- reacting an alkyne, an alkene, and carbon monoxide in the presence of an immobilised cobaltcarbonyl catalyst; or
- reacting an alkyne, an alkene, and carbon monoxide in the presence of an immobilised
- 15 alkynecobaltcarbonyl catalyst.

A further feature is the use of resolved or partially resolved complexes in which the cobalt carbonyl complex [e.g. $\text{LCO}_2\text{CO}_2\text{alkyne}$] or a transition metal complex analogue, is used to give a product that is resolved or partially resolved.

20

- The linking group can be any functional group capable of complexing with the transition metal and joining to the support. The linker group is preferably selected from those ligands known to form a strong bond to the transition metal. Suitable ligands include phosphines, phosphites, and isonitriles. Chiral cobalt carbonyl complexes may be prepared by introducing a chiral
- 25 centre into the linking ligand that connects the support and cobalt.

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A further feature is the use of a resolved or partially cobaltcarbonyl complex containing a chiral centre within the ligand linking the cobalt to the immobilised support, in a Pauson-Khand reaction to give a product that is, preferably, resolved or partially resolved.

- 5 The support to which the catalyst is immobilised may be insoluble, such as a polymer or resin, or soluble, such as a polyethylene glycol (PEG) which can be selectively precipitated as required, or fluorous phases, which show temperature dependent immiscibility with common organic solvents.
- 10 In addition the alkyne and alkene reagent for the Pauson-Khand reaction may form part of the same molecule.

The cobalt carbonyl complex may be prepared by one of the following alternative steps:

- 15 (1) bonding the cobalt complex, which has bound to it through a π -complex bond an alkyne, with the support, where either the cobalt complex or support has a linker group capable of forming a bond or interaction between the cobalt complex and the support;
- (2) bonding the alkyne with the cobalt complex, which is bound to the support via a linker,
- 20 by forming a π -complex between the supported cobalt and the alkyne
- (3) converting an organic molecule attached to the cobalt metal, which is bound to the support via the linker group, to form a π -complex between the supported cobalt complex and the alkyne.

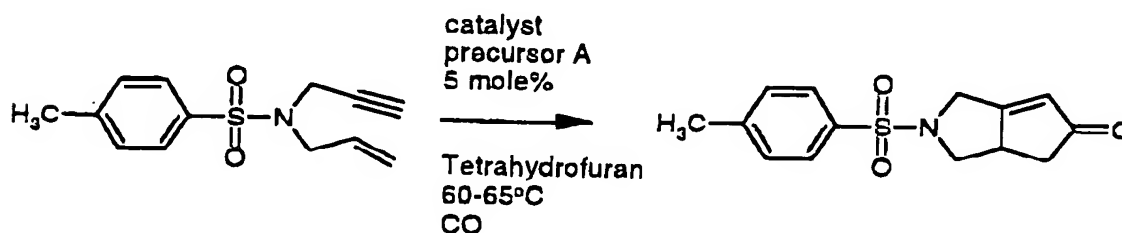
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The invention is illustrated below by the following example where the precursor to the catalytically active species is believed to be polymer-bound dicobalthexacarbonyl, but we do not wish to be limited by this theory.

5 An example of the use of an immobilised catalyst is given in Scheme 2.



Scheme 2

10 Catalyst A precursor resin

Polystyrene-bound diphenylphosphine (2 g, 3.2 mmolP) was suspended at ambient temperature in anhydrous tetrahydrofuran (THF) (15 cm³) and a solution of octacarbonyldicobalt(0) (1.1g, 3.2mmol) in anhydrous THF (5 cm³) was added *via* filter cannula. After 1.5h under constant nitrogen agitation, the mixture was filtered and the resin was washed with alternate aliquots of

15 THF and diethyl ether until the filtrate became colourless. The resulting deep purple beads were dried *in vacuo* to afford the resin complex (2.84 g, 1.0 mmol[Co₂(CO)_x]g⁻¹); $\nu_{\text{max}}(\text{nujol})/\text{cm}^{-1}$ 2074w, 2015msh, 1995ssh, 1979s, 1951m, 1872s; δ_{P} (145.8 MHz)(D₂O capillary lock) 32 [polymer-P(O)Ph₂, 10%], 67 [polymer-(PPh₂)_yCo₂(CO)_x, 90%].

20 Example of catalysis

2,3,3a,4-Tetrahydro-2-[(4-methylphenyl)sulfonyl]-cyclopenta[*c*]pyrrol-5(1*H*)-one.

To a suspension of the catalyst A precursor resin, shown above (24mg, 0.025mmol[Co₂(CO)_m]) in anhydrous THF(5cm³) was added *N*-(2-propenyl)-*N*-(2-propynyl)-4-methylphenylsulfonamide (125 mg, 0.5 mmol) and the resulting mixture was heated to 65 °C under an atmosphere of CO (50 mbar). After 48h the mixture was filtered, the resin was washed with THF (2 x 1 cm³) and the combined filtrates were concentrated *in vacuo*. ¹H-NMR spectroscopy of the pale yellow residue indicated a 1:1 mixture of starting material and product and no by-products. Purification by flash chromatography (SiO₂, 20% EtOAc/hexane) gave the title compound (46mg, 0.167mmol, 33%) as a white solid; mp 147-149 °C; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$ 3058, 1716, 1651, 1350, 1164, 1094, 673; δ_{H} (360 MHz)(CDCl₃) 1.96-2.02 (1 H, m), 2.32 (3 H, s, CH₃), 2.48-2.58 (2 H, m), 3.01-3.36(1 H, m), 3.93-3.98 (2 H, m), 4.27 (1 H, d, *J* 16.5), 5.92 (1 H, s, C=CH), 7.28 (2 H, d, *J* 8, Ar-*H*), 7.66 (2 H, d, *J* 8, Ar-*H*); δ_{C} (¹H) (90MHz)(CDCl₃) 21.6 (CH₃), 39.8 (CH₂), 44.0 (CH), 47.7 (CH₂), 52.5 (CH₂), 126.2 (CH), 127.5 (CH), 130.1 (CH), 133.7 (C), 144.2 (C), 178.6 (C), 207.2 (C=O).